

**REMARKS**

Claims 1-4, 12, 13, 24, and 27-30 are pending in the application. Claims 1-5, 12, 13, 24, and 26-30 were under active consideration. Claims 1, 3, 12, 13, 27, 28 and 29 have been amended to recite "vector construct" in place of "gene delivery vehicle". Support for this amendment is found throughout the specification including, for example, in the original claims and at page 4, lines 13-16 and page 7, lines 15-25.

By amendment herein, claim 30 has been canceled without prejudice or disclaimer, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Thus, claims 1-4, 12, 13, 24 and 27-29 are pending.

**Information Disclosure Statement**

Applicants acknowledge with appreciation that initialed 1449 form of the IDS submitted with the previous response has been returned by Office, indicating that the cited reference has been considered.

**35 U.S.C. § 112, 2<sup>nd</sup> Paragraph**

Claim 30 has been rejected as indefinite for reciting a limitation that had been removed from claim 1 (from which claim 30 depends). (Office Action, page 2).

Applicants have canceled claim 30, without prejudice or disclaimer, thereby obviating this rejection.

**35 U.S.C. § 102(a)**

Applicants acknowledge with appreciation withdrawal of the rejection of claims 1, 4, 24, 26 and 30 under 35 U.S.C. § 102(a).

**35 U.S.C. § 103**

Claims 1-3, 5, 12, 13, and 27-29 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over the reference of Dubensky et al. WO 95/07994 (1995) (hereinafter "Dubensky") in view of Hu et al. (1991) AIDS Res. Hum. Retrovir. 7:615-620 (hereinafter "Hu"). In response to Applicants' arguments, the Office Action alleges that:

- The test for combining references is “not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art [citing *In re McLaughlin*].” (Office Action, page 4).
- Hindsight reconstruction is proper if it does not “include knowledge gleaned only from applicant’s disclosure [citing *In re McLaughlin*].” (Office Action, pages 5-6).
- Dubensky et al. differs from the instant invention only by failing to teach a prime-boost strategy of immunization. (Office Action, page 4)
- The motivation to combine Dubensky and Hu is present because Hu et al. teaches that “boosting vector vaccines with subunit vaccines is more effective than immunization with vector alone.” (Office Action, page 5).

Applicants respectfully traverse the rejection and address each allegation in turn.

#### The Law Governing An Obviousness Inquiry

As the Office notes, statements in the prior art must be considered in the context of the teaching of the entire reference. A rejection of claims **cannot** be predicated on mere identification in a reference of individual components of claimed limitations. In this regard, the Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. *See, e.g., In re Kotzab* 217 F.3d 1365, 55 USPQ2d 1313, 1317 (CAFC 2000, emphasis added):

While the test for establishing an implicit teaching, motivation or suggestion is what the combination of these two statements [in the reference] would have suggested to those of ordinary skill in the art, the two statements cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection **cannot** be predicated on the mere identification [in the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

Virtually all inventions are combinations of old elements. *See, e.g., In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998), noting that the Office cannot rely on a high level of skill in the

art to overcome the differences between the selected elements in the references, it cannot rely on a high level of skill in the art to provide the necessary motivation; *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002), affirming that common knowledge and common sense are not the specialized knowledge and expertise necessary to establish a motivation to arrive at the claimed invention.

Thus, the requirement is not whether each claimed element can be identified individually in a reference but, rather, whether the Office can show “reasons that the skilled artisan, confronted with the same problem as the inventor, and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed.” *In re Rouffet*, 47 USPQ2d at 1458.

Therefore, it is respectfully submitted that the PTO's reliance on *In re McLaughlin*, 170 USPQ 209 (CCPA 1971) is misplaced. *McLaughlin* does not hold that common knowledge is a substitute for evidence, for example as required by 37 C.F.R. 1.104(d)(2). *McLaughlin*, after 32 years, also does not outweigh the many Federal Circuit and CCPA decisions that hold that the prior art must suggest the desirability of the making the claimed combination.

The burden is on the Office to establish that the cited references teach all the elements of the claims and, moreover, suggest the desirability of arriving at the claimed subject matter. *See, e.g., In re Ryckaert*, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). *Amgen, Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991); *In re Laskowski*, 10 USPQ2d 1397, 1399 (Fed. Cir. 1989); and *In re Fulton*, 391 F.3d 1195 (Fed. Cir. 2004), stating that “[t]he question is whether there is something in the prior art as a whole to suggest the desirability”). For the reasons of record and those set forth herein, the Office has not met this burden and, accordingly, the rejection cannot stand.

#### Dubensky Differs In Critical Ways From the Claimed Prime-Boost Methods

As the Office acknowledges, Dubensky does not teach or suggest Applicants' claimed prime-boost methods. Since Applicants' claims relate to prime-boost methods, Dubensky cannot teach, suggest or provide the motivation to arrive at the claimed methods.

For its part, Hu describes administering a live recombinant vaccinia virus expressing HIV envelope glycoproteins in combination with gp160 protein for immunization against HIV. Hu does not teach or suggest the use of retroviral vectors, alphavirus vectors, parvovirus vectors, or

eukaryotic layered vector initiation system vectors for DNA immunization. Nor does Hu teach or suggest the use of antigens from intracellular pathogens such as bacteria, mycobacteria, parasites, hepatitis virus, or feline immunodeficiency virus for immunization against diseases other than HIV.

Therefore, the Office has merely identified the individual elements of the claims in various references without the motivation to combine them into prime-boost methods as claimed. This is improper and, on this basis, the rejection should be withdrawn.

Hu Does Not Provide the Motivation To Combine the References As Set Forth In The Rejection

Despite Dubensky's failure to teach prime-boost methods and Hu's failure to teach or suggest the claimed vectors in prime-boost methods, the Office has maintained that the motivation to combine lies in Hu's teaching that "boosting vector vaccines with subunit vaccines is more effective than immunization with vector alone." (Office Action, page 5).

However, when Hu is read in context, it is clear that Hu's narrow disclosure regarding priming with a live vaccine vector expressing gp160 and boosting with subunit gp160 to produce a high antibody response is **not** a sufficient grounds to assert that the claimed methods are obvious.

First, as noted above and previously, Hu does not teach or suggest any vectors other than live vaccinia. Indeed, Hu is clear that only live recombinant vaccinia vectors were tested (*see*, last sentence of Hu Abstract, emphasis added):

These results also indicate that combined immunization by priming with **live** recombinant virus and boosting with subunit immunogen **may** be more effective than immunization with either immunogen alone.

Second, as Hu teaches, live vaccinia vectors are quite different than other viral vectors, for example in that they themselves elicit an immune response in the subject and in the amount of antigen produced in the subject (Hu, page 617, 2<sup>nd</sup> paragraph of Discussion):

Since both immunogens elicited similar antibody titers after the first immunization, the strong anamnestic response observed only in mice primed with

recombinant vaccinia virus most likely was due to the strong cell-mediated immunity generated by immunization with live viruses. Conversely, subunit protein was more effective as a boosting antigen, probably because of the relatively small amount of antigen produced by the recombinant vaccinia virus in the immunized host.

Given the known differences between viral vectors (which are also highlighted in Hu), Hu would not motivate the skilled artisan to substitute Hu's live vaccinia vector with Dubensky's non-replicating alphavirus vector.

Hu also states that their results are not conclusive and, in fact, contradict the findings of other groups (*see*, above sentence from Abstract noting that live vector prime-protein boost "may" be more effective and page 618, first paragraph of discussion):

Combination immunization with live recombinant vaccinia and HIV-1 envelope antigens has been described in humans and in chimpanzees. However, the results have been variable and no cross-neutralizing antibody has been described.

Thus, by Hu's own terms, the results the authors present are not conclusive – prime-boost with vaccinia and protein **may** be more effective for gp160 or, alternatively, may not actually be more effective in view of the results obtained from other groups.

In sum, Hu does not teach or suggest using non-replicating vectors as claimed by Applicants. The skilled artisan would **not** have viewed live vaccinia vectors as interchangeable with Dubensky's non-replicating alphavirus vectors and, accordingly, would have had no motivation to make the combination set forth by the Office. Nor would the skilled artisan have been motivated to substitute Dubensky's alphavirus vectors for Hu's vaccinia vectors given Hu's equivocation on whether such methods are actually more effective. The alleged motivation to combine (Hu teaches prime-boost methods are better) is not present because Hu is limited to live vaccinia vectors and does not teach or suggest anything regarding non-replicating vectors as disclosed in Dubensky. Without the benefit of Appellants' disclosure, a skilled artisan would have had no motivation and no reasonable expectation of success that substituting Dubensky's non-replicating alphavirus vector for Hu's live vaccinia vector would induce an immune response in accordance with Applicants' methods as claimed.

Applicants respectfully submit that the motivation to combine the references as set forth

in the rejection is not present in Hu.

Reconsideration and withdrawal of the rejection of Claims 1-3, 5, 12, 13 and 27-29 under 35 U.S.C. 103(a) are respectfully requested.

**CONCLUSION**

In light of the above remarks, Applicants submit that the present application is in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

Please direct all further written communications regarding this application to:

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Respectfully submitted,

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